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Evaluation of the Therapeutic Effect of the Antibiotic Meropenem on Liver Histological changes Induced by *Proteus mirabilis* Infection in Laboratory Rats

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Abstract

This study aimed to evaluate the biochemical and histological effect of *Proteus mirabilis* infection and subsequent Meropenem antibiotic treatment on Liver tissue in laboratory rats. Twenty rats were randomized into four groups: a control group injected PBS; an infected group administered *P. mirabilis* inoculum without treatment; and two treatment groups received Meropenem at doses of 10 mg/kg and 30 mg/kg. The results showed a significant increase in liver damage indicators (AST, ALT), as well as the oxidative stress marker MDA, accompanied by a significant reduction in GSH levels in the infected group compared to the control group.Treatment with 10 mg/kg of Meropenem resulted in partial improvement in the measured parameters, while a higher dose of 30 mg/kg resulted in significant and broader enhancements across all vital biomarkers. Histological examinations also revealed clear liver damage in the affected group, while the two treated groups showed gradual improvement, especially at the higher dose, where the histological changes approached normal. These results emphasize the effectiveness of Meropenem in Meropenem in reducing the toxic effects of *P. mirabilis* and highlight its protective role in preserving vital tissues from bacterial-induced damage.

Keywords : Meropenem, Liver, Laboratory rats.، *Proteus mirabilis*

تقييم الاثر العلاجي للمضاد الحيوي Meropenem ضد التأثيرات النّسجية للكبد الناتجة عن الاصابة ببكتيريا *Proteus mirabilis* في الجرذان المختبرية

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الخلاصة

هدفت هذه الدراسة الى تقييم التأثيرات الكيموحيوية والنسجية لبكتيريا *Proteus mirabilis* والعلاج بالمضاد الحيوي Meropenem على أنسجة الكبد في الجرذان المختبرية، شملت التجربة 20 جرذاً تتراوح أوزانهم بين (180-220) غرام وزعوا عشوائياً الى أربع مجموعات: مجموعة السيطرة (حقنت بPBS)، ومجموعة تم حقنها بلقاح بكتيريا *P. mirabilis* دون علاج، ومجموعتين عولجتا بالمضاد الحيوي Meropenem بجرعتين مختلفتين (10 و 30 ملغ/كغم). أظهرت النتائج ارتفاعاً معنوياً في مؤشرات الضرر الكبدي (AST, ALT,) وفي مؤشر الإجهاد التأكسدي MDA، يقابله انخفاض واضح في GSH في المجموعة المصابة مقارنة بالسيطرة. العلاج بجرعة 10 ملغ/كغم من Meropenem أدى الى تحسين جزئي في هذه المعايير، بينما العلاج بجرعة 30 ملغ/كغم أدى الى تحسينات معنوية أوسع في جميع المؤشرات الحيوية. كما كشفت الفحوصات النسجية عن تلف واضح في الكبد للمجموعة المصابة، بينما أظهرت المجموعتان المعالجتان تحسناً تدريجياً، وخاصة عند الجرعة الأعلى حيث أقتربت التغيرات النسجية من الوضع الطبيعي. تشير النتائج الى فعالية المضاد الحيوي Meropenem في الحد من التأثيرات السمية لبكتيريا *P. mirabilis* ودوره في حماية الأنسجة الحيوية من الأذى الناتج عن الإصابة بهذه البكتيريا.

الكلمات المفتاحية ميروبينيم، الكبد، الجرذان المختبرية، بروتيس ميربلس.

Introduction

Proteus mirabilis is a Gram-negative, rod-shaped bacterium that represents a common causative agent of a wide range of clinical infections such as Urinary Tract Infections (UTIs), wounds, burns, prostatitis, meningitis, otitis media, and, rarely, respiratory tract infections (Taher et al., 2025). Moreover, *P. mirabilis* can also cause meningoencephalitis in neonates and plays a role in osteomyelitis (Albujassim et al., 2024). The biofilms of *P. mirabilis* play a crucial role in protecting it against antibiotics as well as host defense mechanisms, posing challenges in treatment due to conferring Multidrug Resistance (MDR) or even Extensively Drug Resistance (XDR) (Mujawar et al., 2021). *Proteus mirabilis* possesses numerous factors that enable it to invade the host and cause disease, including the production of enzymes such as lipase and protease, in addition to hemolysin, the characteristic swarming motility, adhesion to epithelial cells, production of bacteriocins, and the formation of biofilms (Przekwas et al., 2022). The enzyme urease is also considered an important virulence factor for *P. mirabilis* it is a metalloenzyme containing nickel, which is essential for the formation of the enzyme's active sites (Chakkour et al., 2024). Antibiotics remain a cornerstone of modern medicine, having effectively contributed to the reduction of bacterial

infections and associated mortality rates (Cook and Wright, 2022). However, their excessive and uncontrolled use has accelerated the emergence of resistant bacterial strains, representing a significant global health challenge (Aslam et al., 2024). The antibiotic Meropenem, which belongs to the carbapenem class, is an effective treatment against many bacterial strains resistant to common antibiotics, including *P. mirabilis*. Its therapeutic effect is attributed to its ability to inhibit bacterial cell wall synthesis, leading to the eradication of bacterial cells and the reduction of their toxic effects. Despite the widespread use of Meropenem in clinical and research applications, studies addressing its impact on biochemical disturbances and histopathological changes remain limited (Alqurashi et al., 2022; Shaaban et al., 2022).

Based on the above, the present study aims to evaluate the effect of *Proteus mirabilis* infection on the liver of laboratory rats, while examining the therapeutic role of Meropenem administered at specific doses, and comparing the results with control groups to assess its efficacy in mitigating pathological effects. This may contribute to advancing scientific knowledge and guiding future therapeutic practices in both human and veterinary medicine.

Materials and Methods

Preparation of Bacterial Vaccine

P. mirabilis inoculum was prepared by culturing the bacteria in a 250 ml glass flask containing 100 ml of sterile nutrient broth medium. The medium was inoculated with the isolated and purified bacteria and incubated for 24 hours. The appearance of turbidity in the medium indicates bacterial growth and the bacterial inoculum was obtained. A series tenfold serial dilutions, and 0.5 ml of the seventh dilution was plated on nutrient agar to determine the bacterial density by counting the number of colonies growing on the surface of the medium. This dilution was used for intraperitoneal injection (IP) in laboratory rats to induce infection.

Preparing of the treatment

Meropenem antibiotic powder was used to treat animals infected with *P. mirabilis*. Two different doses were prepared. The low dose was prepared by dissolving 12.5 mg of powder in 2.5 ml of sterile normal saline, resulting in a treatment concentration of 10 mg/kg. The high dose was prepared by dissolving 37.5 mg of powder in 2.5 ml of sterile normal saline, resulting in a concentration of 30 mg/kg.

Laboratory Animals Used in the Study

This experiment was conducted in the animal house of the Department of Biology, College of Education for Pure Sciences, University of Anbar, which was fully equipped with all necessary supplies for the scientific study. This experiment involved 20 male Swiss Sprague Dawley rats, weighing between 180 and 220 grams and aged between 6 and 8 weeks.

The animals were housed in plastic cages with metal lids specially prepared for this purpose. They were maintained under controlled laboratory conditions with a light cycle of 11 hours of light and 13 hours of darkness. The temperature was regulated at 22 ± 2°C. Cages were cleaned and sterilized, with sawdust replaced twice a week. A commercially prepared diet was provided, with food and water available ad libitum throughout the study. The animals were acclimatized for two weeks to the new environment to ensure their health status and freedom from diseases before the experiment commenced.

Experimental Design

The animals were randomly assigned into four groups, with five animals in each group of approximately similar body weights, as follows:

Group 1 (Control group): Received a single intraperitoneal (IP) injection of 0.5 ml phosphate-buffered saline (PBS).

Group 2 (Infected group): Infected with *P. mirabilis* via IP injection. Each animal received 0.5 ml of the previously prepared bacterial suspension, taken from the seventh dilution. Injections were administered four times over a period of 7 days to ensure consistent infection.

Group 3 (Infected + Low-dose treatment): Infected with *P. mirabilis* as in Group 2, followed 3 hours later by treatment with a low dose (10 mg/kg) of Meropenem. The bacterial suspension was injected twice over 14 days, and the antibiotic was administered five times during the same period.

Group 4 (Infected + High-dose treatment): Infected with *P. mirabilis* as in Group 2, followed 3 hours later by treatment with a high dose (30 mg/kg) of Meropenem. The bacterial suspension was injected twice over 14 days, and the antibiotic was administered five times during the same period.

Collection Blood Samples

Blood samples were collected directly from the heart using a sterile 5 ml syringe via the heart puncture technique. The samples were transferred into anticoagulant-free test tubes and left at room temperature for 15–20 minutes to

allow clot formation. Subsequently, the tubes were centrifuged at 3000 rpm for 15 minutes to separate the serum, which was then used for biochemical analyses.

Biochemical Tests

The following liver tests, Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST), were performed according to the method of (Reitman and Frankel, 1957) as specified in the Kit protocol. Oxidative stress markers, including malondialdehyde (MDA) activity, were evaluated based on the method of Ohkawa et al. (1979), following the kit instructions. Additionally, the level of the antioxidant glutathione (GSH) was measured according to the method of Sedlak and Lindsay (1968), in accordance with the kit's protocol.

Tissue sampling

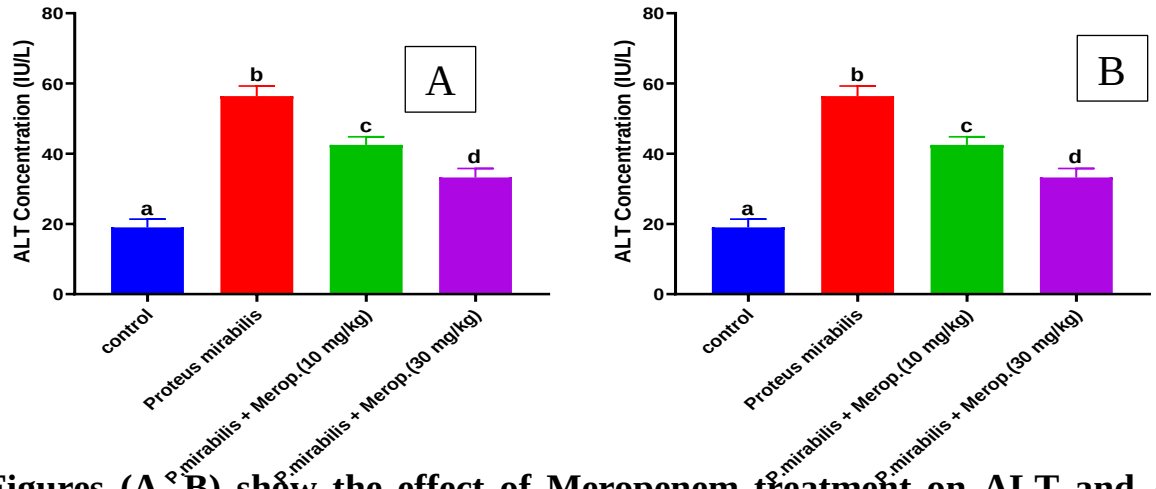
Fresh rat Liver samples were excised and fixed in 10% formalin. They were then dehydrated using varying concentrations of ethanol (70%, 80%, 90%, and 100%). The samples were then prepared for embedding in paraffin wax. Sections were cut using a rotary microtome at 5–7 µm thickness and stained with standard hematoxylin and eosin (H&E). The histological sections were examined using a light microscope equipped with a digital camera.

Statistical analysis

The results were statistically analyzed using GraphPad Prism V.8 to determine significant differences among treatment groups. One-way analysis of variance (ANOVA) was performed, followed by calculation mean and standard at a significance level of $P \leq 0.05$, based on standard statistical procedures. Statistical analysis was conducted according to Duncan's multiple range test (Duncan, 1995).

Results and discussion

Figures (A and B) illustrate the concentration levels of AST and ALT enzymes. It is evident that there is a significant increase in enzyme levels in Second Group, which was injected with the *P. mirabilis* bacterial inoculum, compared to the control group. The figures also show changes in the same enzyme levels in Third Group, which received the bacterial inoculum followed by Meropenem at a dose of 10 mg/kg, where a reduction in AST and ALT levels was observed compared to the infected group. In Forth Group, which received the bacterial inoculum followed by Meropenem at 30 mg/kg, a greater decrease in enzymes levels was noted compared to Second Group.

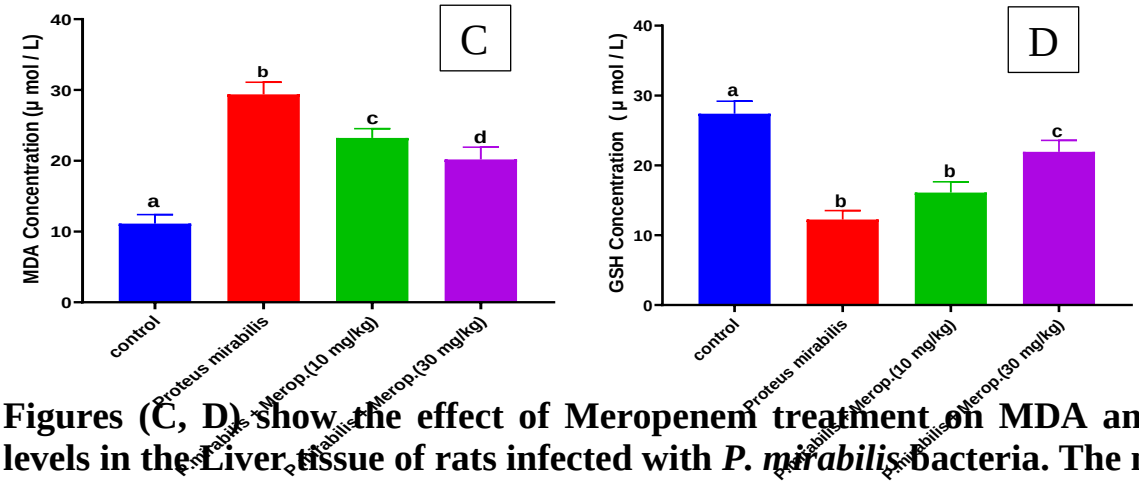


Figures (A, B) show the effect of Meropenem treatment on ALT and AST levels in the Liver tissue of rats infected with *P. mirabilis* bacteria. The number of animals in each group was (5). Different English letters indicate significant differences at the probability level ($P \leq 0.05$).

The results showed a significant increase in ALT and AST enzyme levels in Second Group (infected), which was injected with *P. mirabilis*, compared to the control group. This elevation indicates hepatocellular damage resulting from the bacterial infection. Such systemic infection triggers the host inflammatory immune response, stimulating the production of pro-inflammatory cytokines such as TNF-α (Tumor Necrosis Factor-α), IL-6 (Interleukin-6), and IL-1β (Interleukin-1β) (Huang et al., 2017). The bacterial infection also causes hepatocyte injury via endotoxins (LPS) Lipopolysaccharides produced by the bacteria, which bind to TLR4 (Toll-Like Receptor 4) on liver cells. This interaction initiates a cascade of inflammatory reactions and cytokine release, leading to the recruitment of immune cells to the liver. These cells secrete reactive oxygen species (ROS) and digestive enzymes that contribute to hepatic tissue destruction and increased hepatic capillary permeability, resulting in elevated ALT and AST levels due to their leakage from hepatocytes into the bloodstream (Jaeschke, 2000). The results demonstrated a progressive improvement and reduction in ALT and AST levels in Third and Forth Group , particularly in Forth Group, which received the higher Meropenem dose (30 mg/kg). This indicates the efficacy of Meropenem in mitigating hepatocellular damage by combating the bacterial infection. Consequently, this treatment led to a reduction in bacterial load and associated toxins, decreased the inflammatory response, and improved liver function (Onorato et al., 2022), resulting in lower ALT and AST levels compared to the infected group.

The results shown in Figures (C and D) showed a significant increase in the concentration of MDA as well as a significant decrease in the concentration of

GSH for the second group that was injected with the *P. mirabilis* bacterial vaccine compared to the control group. As for the third group, which was injected with the bacterial vaccine and then with the antibiotic Meropenem at a concentration of 10 mg/kg, there was a significant decrease in the concentration of MDA and a significant increase in the concentration of GSH compared to the second group. While the results for the fourth group, which was injected with the bacterial vaccine and then with the antibiotic Meropenem at a concentration of 30 mg/kg, showed a significant decrease in the concentration of MDA as well as a significant increase in the concentration of GSH compared to the second group.



Figures (C, D) show the effect of Meropenem treatment on MDA and GSH levels in the Liver tissue of rats infected with *P. mirabilis* bacteria. The number of animals in each group was (5). Different English letters indicate significant differences at the probability level ($P \leq 0.05$).

The results showed a sharp increase in the MDA value, which is a byproduct of lipid peroxidation and is used as a biomarker of oxidative stress and cell membrane damage. It was very high in the second group (infected with bacteria), indicating severe oxidative stress resulting from bacterial inflammation, as these bacteria contain LPS (lipopolysaccharides) in their cell wall, which stimulates innate immune receptors such as TLR-4, leading to the activation of macrophages and neutrophils. This may be attributed to the generation of free radicals (ROS) that attack unsaturated fatty acids in cell membranes, causing widespread oxidative damage and increased lipid peroxidation resulting from the severe immune response (Mittal et al., 2014). As for the third and fourth groups (the treatment group), a decrease in MDA levels was observed, indicating a partial improvement in the oxidative status. This was more evident in the fourth group, demonstrating the role of this treatment, Meropenem, and its positive effect in reducing lipid peroxidation. This may be attributed to reducing the bacterial load, stopping the stimulation of TLR-4 receptors by bacterial LPS, reducing the activation of the

immune system, reducing the secretion of inflammatory cytokines, and thus reducing ROS types (Feng et al., 2025). These results indicate the effectiveness of this treatment in protecting and maintaining the safety of cells and tissues during bacterial infection. As for the antioxidant GSH, which is one of the most important endogenous antioxidants in the body, as it works to neutralize free radicals and protect cells from oxidative damage, the results showed a sharp decrease in GSH levels in the second group (infected with bacteria), indicating an intense stimulation of oxidative stress caused by the innate immune response against bacterial LPS, which leads to increased ROS production within immune cells such as neutrophils and macrophages. This may lead to excessive consumption of GSH stores in an attempt to defend the cell against oxidative damage (Al-Obeidi et al., 2024). Bacterial infection may be accompanied by excessive activity of oxidative enzymes, and these enzymes produce large amounts of ROS, thus rapidly depleting GSH. In addition, inflammatory cytokines activate ROS-producing pathways and inhibit the expression of enzymes responsible for GSH regeneration, which weakens the body's ability to regenerate it. These factors may lead to an imbalance in oxidative balance (Labarrere and Kassab, 2022). As for the third group, the results showed a slight improvement compared to the second group. Meanwhile, the results for the fourth group showed a significant increase in GSH compared to the infected group, indicating a partial recovery of the antioxidant system. Meropenem treatment, especially at the high dose, reduced the bacterial load (Yayan et al., 2016), leading to a decrease in the production of free radicals (ROS). This decrease reduces oxidative stress on cells, allowing for the resynthesis of GSH. It also contributed to strengthening cellular defenses, restoring oxidative balance, suppressing infection, and stabilizing the cell membrane.

Histological examination of the liver in the control group, which was injected with phosphate-buffered saline (PBS) (Image 1), showed Hepatocytes (HC) that were polygonal in shape and of normal size. The cell nuclei were basophilic and spherical, with some cells containing two nuclei in the cytoplasm. The hepatocytes were arranged in radial rows resembling honeycomb patterns toward the Central Vein (CV). The Sinusoids (S) contained Kupffer Cells (KC). In Second Group, which was injected with the *P. mirabilis* bacterial inoculum (Image 2 and 3), the Central Vein (CV) was surrounded by disorganized Hepatocytes (HC), with cell Degeneration (D). Additionally, Thickening of the vessel Walls (TW), vascular Congestion (CON), Sinusoidal dilation (S), Bile Duct dilation (BD), and Inflammatory Infiltration (IL) were observed. For Third Group, which received the bacterial inoculum followed by Meropenem at 10 mg/kg (Image 4 and 5), microscopic examination revealed Sinusoidal dilation (S), an increased number of Kupffer Cells (KC), vascular Congestion (CON), deposition of Necrotic Material

(NM), Hepatocyte Hypertrophy (HT), and cellular Degeneration (D). In Forth Group, which received the bacterial inoculum followed by Meropenem at 30 mg/kg (Image 6 and 7), the liver histology showed Hepatocytes (HC) with normal morphology, Kupffer Cells (KC), mild vascular Congestion (CON), and slight Inflammatory Infiltration (IL). This therapeutic group demonstrated the best results, with histological features closely resembling the control group, except for minor tissue changes.

Image (1) Cross section of the liver of the control group showing the central vein (CV), hepatocytes (HC), sinusoids (S), and Kupffer cells (KC) (H & E stain. 400X).

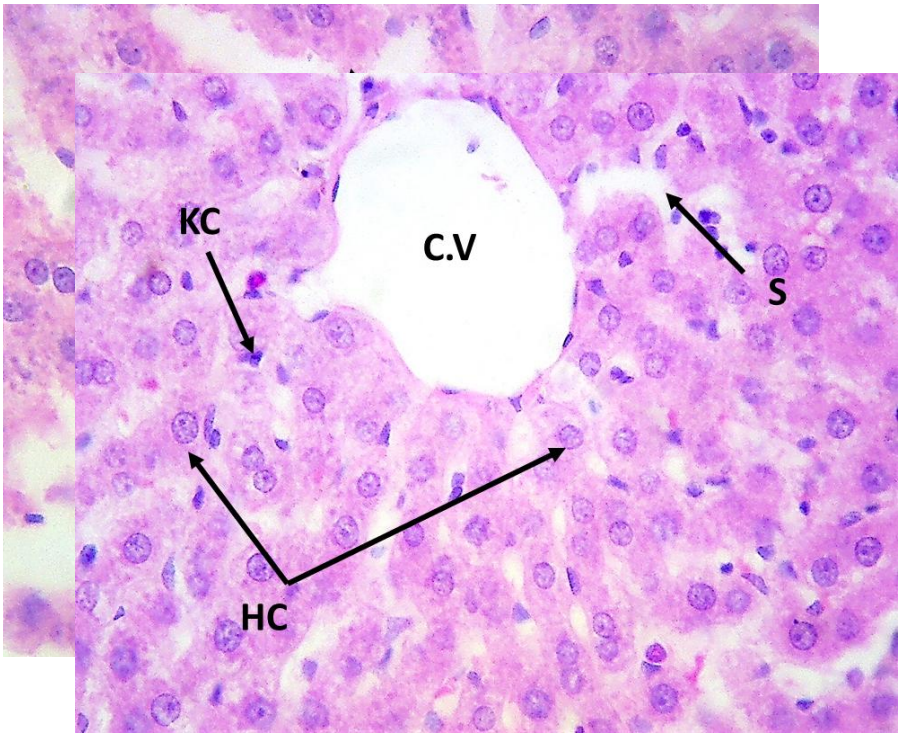


Image (2) Cross section of the liver of Second group showing the central vein (CV) and surrounding hepatocytes (HC) in a disorganized and irregular manner, cellular degeneration (D), and dilatation of the sinusoids (S). (H&E stain. 400X).

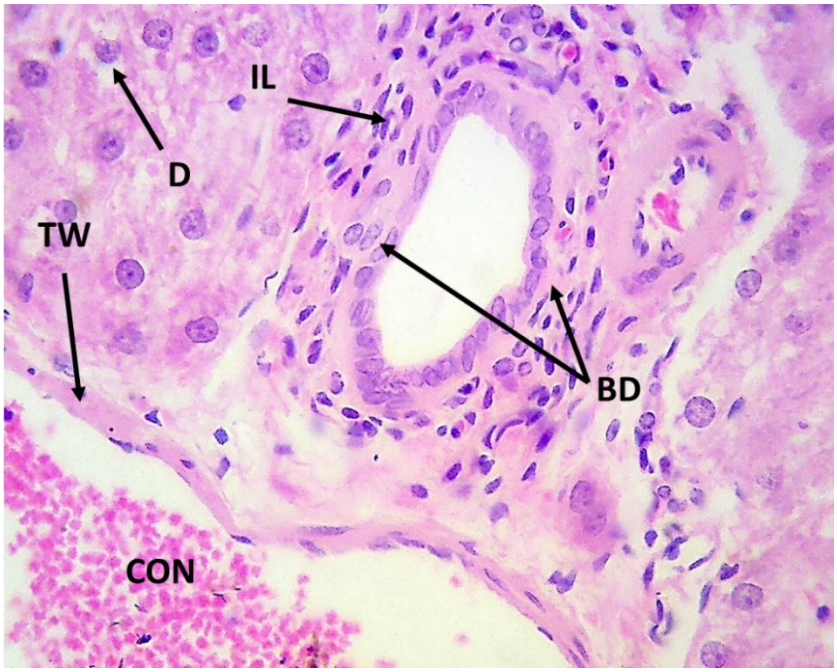


Image (3) Cross section of liver of Second group showing congestion (CON), bile duct dilatation (BD), inflammatory infiltrate (IL), cell degeneration (D), and vein wall thickening (TW). (H&E stain. 400X).

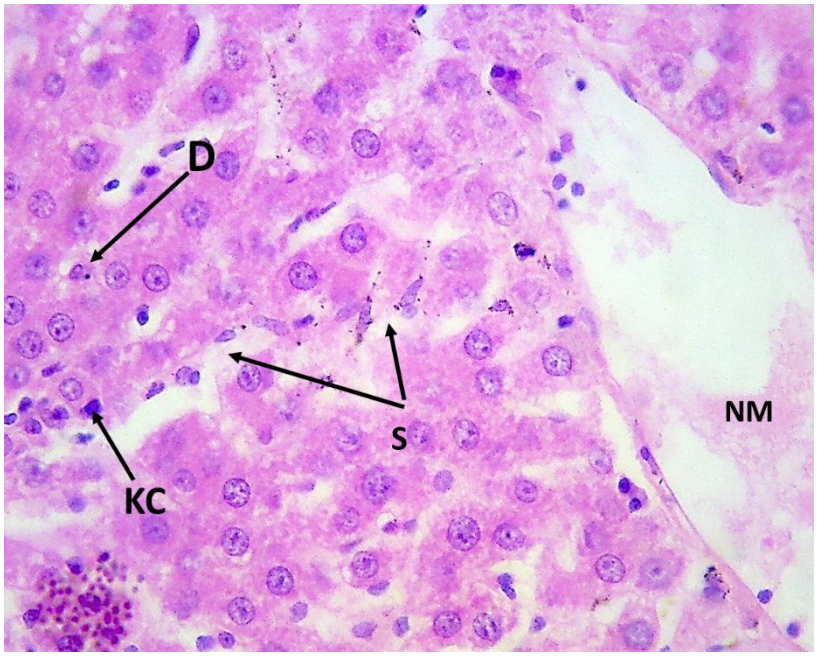


Image (4) Cross section of liver of Third group showing dilated sinusoids (S), increased Kupffer cells (KC), deposition of necrotic material (NM), and cell degeneration (D). (H&E stain. 400X).

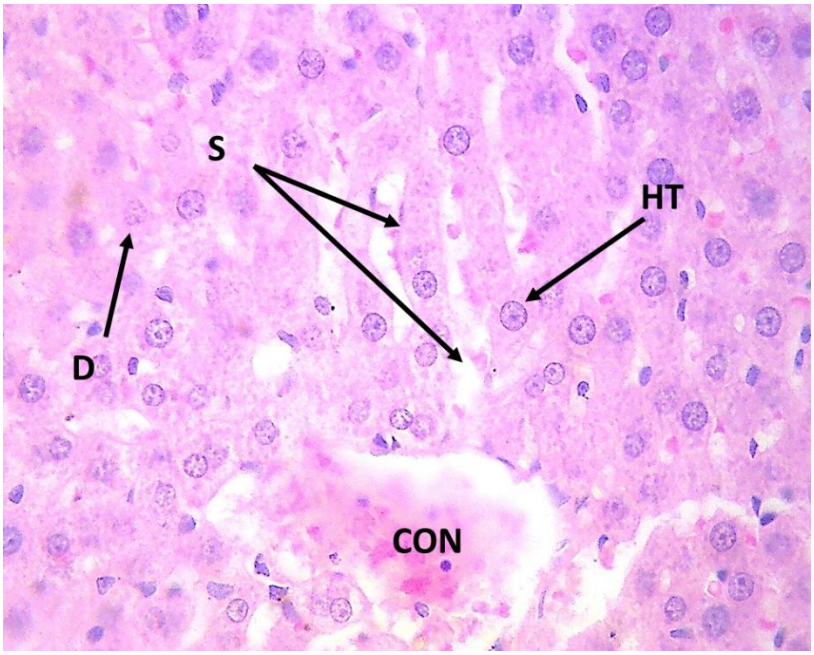


Image (5) Cross section of Third group liver showing sinusoidal dilatation (S), congestion (CON), cellular enlargement (HT), and cell degeneration (D). (H&E stain. 400X).

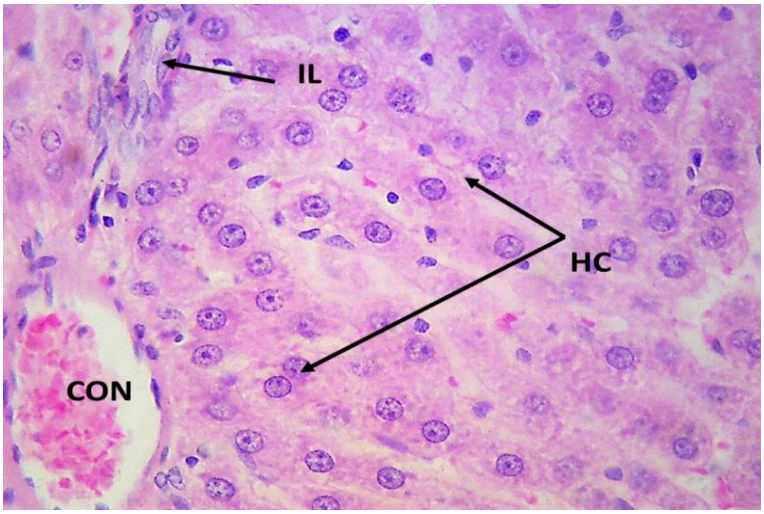


Image (6) Cross section of Forth Group liver showing hepatocytes (HC), congestion (CON), and inflammatory infiltrate (IL). (H&E stain. 400X).

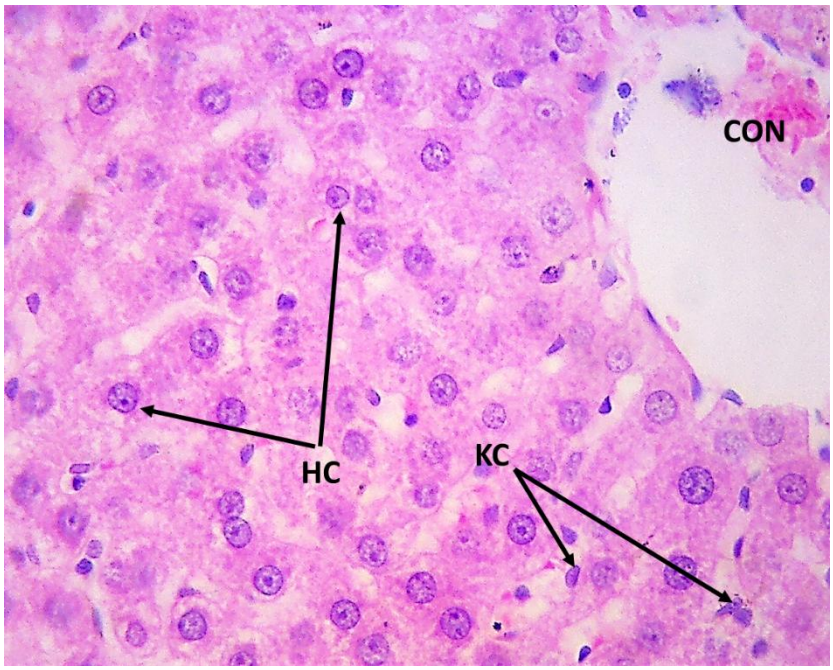


Image (7) Cross section of Forth Group liver showing hepatocytes (HC), congestion (CON), and Kupffer cells (KC). (H&E stain. 400X).

The histological results of the liver samples from rats in the present study revealed distinct differences in liver tissue architecture among the four experimental groups, reflecting the tissue effects of *Proteus mirabilis* as well as the therapeutic role of Meropenem at different doses in mitigating these pathological changes.

In the control group, which was injected only with PBS, the histological examination showed normal liver tissue architecture. Hepatocytes were arranged radially around the central vein, characterized by acidophilic cytoplasm and basophilic, spherical nuclei, with some cells being binucleated, consistent with the normal hepatic tissue pattern in rats. The sinusoids were regularly dilated and contained Kupffer cells (KC). This normal tissue organization corresponded with functional results, as reflected by normal ALT and AST enzyme levels, indicating intact hepatocyte membranes and the absence of cellular degeneration or necrosis, confirming that the experimental factor (injection alone, without bacteria or treatment) had no toxic effect on the liver.

Histological sections of Second Group (infected with *Proteus mirabilis*) revealed pronounced pathological tissue changes, including disruption of the radial arrangement of hepatocytes around the central vein, evident cellular degeneration (D), sinusoidal dilation (S), vascular congestion (CON), and thickening of vessel walls (TW). Additionally, inflammatory infiltration (IL) was observed around the vessels, along with bile duct dilation (BD). These histological changes were accompanied by a significant elevation in ALT and AST levels, indicating hepatocyte membrane damage and leakage of enzymes into the bloodstream. These tissue alterations can be explained by known mechanisms of *P. mirabilis* pathogenicity, including the release of endotoxins (LPS), which trigger a systemic inflammatory response leading to hepatocyte membrane injury. Furthermore, bacterial proteases may induce pore formation in cell membranes, resulting in cellular content leakage, decreased membrane potential, metabolic inhibition, and cellular necrosis with associated inflammation. The metalloprotease ZapA (Zinc-dependent protease A), a major component of *P. mirabilis*, can invade host tissues and cause damage by degrading gelatin and fibronectin in the extracellular matrix (ECM), facilitating bacterial penetration into deeper tissues (Al-Obeidi et al., 2021). Moreover, microvascular disturbances caused by vascular dilation and congestion (CON) may contribute to local hypoxia and exacerbate degeneration (N).

In Third Group, the results indicated a partial improvement in liver tissue structure compared to Second Group however, signs of damage were still noticeably present. The observed changes included sinusoidal dilation (S), vascular congestion (CON), an increased number of Kupffer cells (KC), deposition of necrotic material (NM), hepatocyte hypertrophy (HT), and cellular degeneration (N). This suggests that the low dose of Meropenem may have been insufficient to fully mitigate the effects of the bacterial infection or to completely control inflammation (Patel et al., 2007). Some bacterial colonies and their secreted toxins might still have been active, and the treatment concentration may not have been adequate to eradicate the bacteria and their harmful effects, explaining the persistence of cellular damage. Nevertheless, the increase in Kupffer cells indicates an ongoing immune response and an attempt by the liver to restore homeostasis.

In contrast, Forth Group showed clear improvement in liver histology, with hepatocytes regaining their normal, regular morphology, while mild vascular congestion (CON) and slight inflammatory infiltration (IL) remained. The sinusoids (S) and Kupffer cells (KC) appeared nearly normal. These findings demonstrate the efficacy of the high-dose Meropenem treatment in controlling the bacterial infection, either by killing the bacteria or inhibiting their growth, thereby mitigating their harmful effects, reducing inflammation and tissue damage, and

allowing the liver to restore its normal function (Florea et al., 2022). This high dose likely effectively reduced bacterial impact, decreasing the release of cytokines and bacterial toxins responsible for cellular injury Consequently, these findings demonstrate that *P. mirabilis* infection induced severe hepatic tissue damage, characterized by disruption of normal tissue architecture and the presence of inflammatory and degenerative markers (Anifowose et al., 2024).

Number of Bacteria in Bacterial Vaccine

After preparing the bacterial inoculum, the bacterial count was calculated using colony-forming unit (CFU) method, where 0.5 ml of the bacterial inoculum at the seventh dilution contained 95×10^7 CFU.

Conclusion

Proteus mirabilis infection induced pronounced biochemical and histological changes in the liver, manifested by elevated liver enzyme levels and increased oxidative stress markers. In contrast, treatment with the antibiotic Meropenem demonstrated notable therapeutic efficacy, reflected by a reduction in harmful biochemical indicators and improvement of the hepatic tissue architecture.

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